REMARKS

This is in response to the Official Action of September 26, 2006.

Newly presented claims.

Claims 1-28 are pending in the application prior to the entry of this amendment.

New claims 29-31, dependent upon claim 1, are directed to each of the conditions set forth in claim 1 (reperfusion injuries, osteoporosis, bone metastasis), but in individual form.

New claim 32, also dependent upon claim 1, is directed to a Markush group of potential active compounds. The group of compounds in claim 32 is supported by the Table set forth in the specification at pages 42-89.

New claims 33-35 correspond to claims 29-31 except that they are dependent upon claim 32.

These claims are added to complete the record.

Information disclosure statement and supplemental information disclosure statement.

In the Official Action, it is noted that document WO 01/30778 was not present in the file and was not considered. In the supplemental Information Disclosure Statement submitted concurrently herewith, two family members of that record, US Patent No. 6,608,072 and EP 1224185, are provided to complete the record.

It is also noted that the "International Search Report" was not present in the file. This search report is submitted concurrently herewith to complete the record.

In addition, it is noted that no translation was provided for WO 01/00610. Hence, two English-language counterparts, US 6,358,978 and EP1194425 (claims only) are provided concurrently herewith, to complete the record.

It is also noted that no translation was provided for WO 01/30774. Hence, an English-language counterpart, Australian patent No. AU 781443B, is submitted concurrently herewith.

Claims rejections—35 USC 112.

Claims 1-28 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply

with the enablement requirement. For the reasons set forth below, reconsideration and withdrawal of this rejection is respectfully requested.

The first paragraph of 35 USC 112 requires that a patent teach how to make and use the claimed invention without **undue experimentation.** MPEP 2164.01. As further noted: "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *Id.* It is well settled that "a patent need not teach, and preferably omits, what is well known in the art". Further, it is well settled that statements made in a specification must be taken as true "unless there is a reason to doubt the objective truth thereof." MPEP 2164.04

In determining whether or not the enablement is satisfied in any particular case, reference is typically made to the factual inquiries specified in *In re Wands*, and enumerated in MPEP 2164.01(a), as follows:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

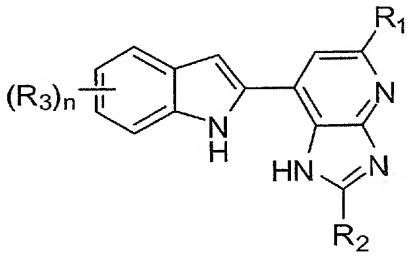
In this case, when the *Wands* factors are evaluated, it is respectfully submitted that the enablement requirement is clearly satisfied. Hence, each of these factors is discussed in greater detail below.

(A) The breadth of the claims. It is respectfully submitted that the claims in this case are well focused and that this factor weighs in favor of applicants.

First, the claims are directed to three particular disorders: the treatment of "reperfusion

injuries, osteoporosis and/or bone metastasis". The number of disorders with which applicants are concerned is not overly broad, and this weighs in favor of applicants.

Second, the claims have a well-defined core structure:



Note the lack of any variable substituents in the core structure, and note indeed the specification of two separate hetero ring structures linked by a specific covalent linkage. The well-defined core structure weighs in favor of applicants.

Third, the Markush groups R_1, R_2 and R_3 on the core structure are generic in nature. However, the location of R_1 and R_2 is well-specified. While R_1, R_2 and R_3 are generically defined, it is respectfully submitted that this does not outweigh the other factors noted above, particularly in light of the factors discussed in further detail below.

(B) The nature of the invention. This factor (which here overlaps with "The state of the prior art" discussed below), weighs strongly in favor of applicants. The invention concerns the treatment of three disorders with small organic compounds.

The first of these disorders, reperfusion injuries, is a long-established area in which numerous patents have issued. A few examples of patents in this area are:

US Patent No. 4,877,810, *Protection of heart tissue from reperfusion injury*;

US Patent No. 4,939,146, *Method for alleviating ischemic-reperfusion injury*;

US Patent No. 4,999,365, *Method of reducing reperfusion injury with imidazol-2-thiones*; and

US Patent No. 5,002,965, *Use of ginkgolides to prevent reperfusion injury in organ transplantation.*

The long-established nature of this subject matter in the issued patent literature weighs strongly in favor of applicants

The second and third of these disorders, osteoporosis and bone metastasis, are also well established. In addition, these two disorders are logically related methods of treatment. Examples of patents with issued method of treatment claims, in which "osteoporosis" and "bone metastasis" are grouped together *in the same claim* for treatment with a particular intervention, include:

US Patent No. 7,186,683 *Use of GLP for the treatment, prevention, diagnosis, and prognosis of bone-related and nutrition-related disorders* (*see, e.g.*, claim 3);

US Patent No. 6,884,804, *Inhibitors of Src and other protein kinases* (*see, e.g.*, claim 24);

US Patent No. 6,747,053, *Heteroaryl nitriles* (*see, e.g.*, claim 36);

US Patent No. 6,693,108, *Inhibitors of c-JUN N terminal kinases (JNK) and other protein kinases* (*see, e.g.*, claim 11); and

US Patent No. 6,110,967, *Epoxysuccinamide derivative or salt thereof* (*see, e.g.*, claims 21-23)

Again, the established nature of these two subject matters, here taken together with the well-established interrelationship of these two subject matters in the issued patent literature, weighs strongly in favor of applicant.

The patent references noted above are submitted concurrently herewith in a supplemental Information Disclosure Statement.

(C) The state of the prior art. It is respectfully submitted that this factor weighs strongly in favor of applicant for the same reasons as discussed in connection with "*(B) The nature of the invention*" above. The state of the prior art also resolves the issue of "correlation" in applicants favor, as discussed further in section "*(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure*" below.

(D) The level of one of ordinary skill. The level of skill in the applicable art or arts being high, this factor weighs strongly in favor of applicant. Applicants wish to point out that, to the extent the present invention involves multiple fields (*e.g.*, synthesis of compounds, formulation into suitable dosage form, and screening in biological systems), then the applicants need only

enable the *specialist in each art* to carry out that aspect of the invention on which he or she is most qualified to work. *See, e.g., In re Naquin,* 398 F.2d 863, 866, 158 USPQ 317, 319 (CCPA 1968).

(E) The level of predictability in the art. The biological sciences are generally categorized as "unpredictable". However, it has been repeatedly emphasized that the issue is not predictability *per se*, but the type of work and experimentation acceptable in the particular field, or fields, of the invention. In *In re Angstadt,* the Court of Customs and Patent Appeals cautioned that:

> If [our prior decision stands] for the proposition that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction,* whether the claimed product will be obtained,... then *all* "experimentation" is "undue," since the term "experimentation" implies that the success of the particular activity is *uncertain.* Such a proposition is contrary to the basic policy of the patent act...."

In re Angstadt, 537 F. 2d 498, 503, 190 USPQ 214, 219 (CCPA 1976). The court went on to emphasize that "the key word is "undue," not "experimentation." *Id* at 504, 190 USPQ at 219.

In this field, synthesis, formulation, and screening is all an accepted part of the development process. The US Court of Appeals for the Federal Circuit has caution that:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

(F) The amount of direction provided by the inventor. The inventors provide considerable direction and this factor weighs in favor of applicant. The amount of direction regarding the selection and synthesis of specific active agents is high. The amount of direction regarding the preparation of pharmaceutical formulations is *(a)* considerable (see pages 28-39 of the specification, and *(b)* consistent with what is typical in the patent literature for methods of treating diseases of this type, with organic compound active agents. A straightforward screening

procedure to aid in selecting particular compounds is given, as discussed further below. These factors all weigh in favor of the applicant.

(G) The existence of working examples. The present application has a lengthy and substantive Examples section spanning pages 41-187 of the specification, and this should weigh strongly in favor of applicants. It is noted that these examples are concerned with the synthesis of compounds, but synthesis of compounds is an aspect of the invention noted by the Examiner. A straightforward screening assay is given on page 187 of the specification (as discussed further below). These factors weigh in favor of applicant.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. The "Official Action" raises the issue of "correlation" in connection with the biological assay provided on page 187 of the instant application. When considered in light of the state of the art, this assay assists the skilled person or persons in practicing the present invention without undue experimentation.

The present invention concerns inhibitors of cell adhesion molecules (specification, page 1, paragraph 3). The assay on page 187, adapted to a 96 well plate and hence suitable for high-through-put screening, screens for compounds that influence E-selectin expression.

The selectins as a target for therapeutic intervention in the treatment of cancer and other diseases was known well before the filing date of the present application. For example, S. Hakomori describes blocking of transmembrane signaling for expression of P and E-selectin as a mechanism for inhibition of metastasis in 1996 (S. Hakimori, Tumor Malignancy Defined by Aberrant Glycosylation and Sphingo(glyco)lipid Metabolism, *Cancer Research* **56**, 5309-5318 (1996) (copy submitted concurrently herewith). The ongoing interest in this intervention strategy is demonstrated by C. Dimitroff et al., Identification of Leukocyte E-Selectin Ligands, P-Selectin Glycoprotein Ligand-1 and E-Selectin Ligand-1, on Human Metastatic Prostate Tumor Cells, *Cancer Research* **65**, 5750-5760 (2005) (copy submitted concurrently herewith).

The correlation of activity between selectins and the therapeutic treatment of a variety of diseases, including cancer, osteoporosis, and reperfusion injury, was well established in the

issued patent literature before the filing date of the instant application. Examples of patents demonstrating this correlation include but are not limited to:

US Patent No. 5,618,785, *Peptide inhibitors of selectin binding* (*see, e.g.,* claim 39);

US Patent No. 5,632,991, *Antibodies specific for E-selectin and the uses thereof*; (*see, e.g.,* claim 10);

US Patent No. 5,728,685, *Methods of treating inflammation using cell adhesion inhibitors* (*see, e.g.,* claim 2 (concerns both reperfusion injury and cancer))

US Patent No. 6,048,841, *Peptidyl compounds (see, e.g.*, claim 10 (cancer and reperfusion injury) and claim 12 (osteoporosis))

(copies submitted concurrently herewith). The provision of the screening assay in the instant case provides skilled works with a means of expeditiously screening compounds for activity, which activity is correlated with therapeutic usefulness by the literature prior to the filing of the instant application. Hence, this factor weighs in favor of the applicants.

Conclusion regarding enablement. When the evidence as a whole is considered, it is respectfully submitted that the present invention satisfies the requirement for enablement set forth in the first paragraph of 35 USC 112, and it is respectfully submitted that this rejection should be withdrawn.

Conclusion

It is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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